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EDITORIAL COMMENT

Fibrates and Cardiorenal Outcomes*

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The dyslipidemia associated with chronic kidney disease (CKD) is characterized by elevated levels of triglycerides (TG) and lower concentrations of high-density lipoprotein cholesterol (HDL). Treatment options include an array of therapies, all of which have benefit-to-risk relationships that deserve careful consideration. Fibrates or fibric acid derivatives induce lipoprotein lipolysis by acting as ligands to the peroxisome proliferator–activated receptor alpha (α) subunit, activating the transcription of multiple genes including those that up-regulate lipoprotein lipase, a catabolic enzyme (1). Increased lipoprotein lipase enhances the metabolism of TG-rich particles, including chylomicrons and very low-density

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lipoprotein (VLDL) (2,3). In addition, peroxisome proliferator–activated receptor stimulation influences multiple pathways in reverse cholesterol transport (1). Triglycerides are also a substantial component of intermediate-density lipoprotein (IDL), and comprise ~50% of low-density lipoprotein (LDL) particles. Fibric acid derivatives reduce fasting TG values by 15% to 50% (depending on baseline level—greater reductions with higher levels), LDL by 8%, and raise HDL by 9% (4). In conjunction with a statin, the amount of TG lowering is approximately doubled with the addition of the fibrate. Fibrates decrease the TG concentration of LDL particles while increasing the TG content of LDL particles (5). Thus, the mean size of LDL particles increases, with a substantial reduction in the number and proportion of small dense LDL particles (4,6). When there is fasting hypertriglyceridemia (TG >200 mg/dl) and the TG concentration is sufficiently lowered by a fibrate, large randomized trials have shown relative risk reductions of 27% to 65% in cardiovascular (CV) endpoints including nonfatal myocardial infarction and CV death (4). Conversely, when TG concentrations are normal (<150 mg/dl), further reductions do not measurably influence LDL particle size or number and as a result, there is no CV benefit. Thus, fibrates are a second-line preventive therapy after statins in patients with residual elevations in non-HDL cholesterol and hypertriglyceridemia in the general population, however, their role in patients with CKD has yet to be defined given their unique effects in this subgroup (7).

Reduced renal blood flow and glomerular filtration have been a consistent secondary effect seen with fibric acid derivatives (8). Reductions are mild and reverse within 2 weeks of drug discontinuation (9). It has been postulated that this effect is due to a reduction in the production of vasodilatory renal prostaglandins (10). In this issue of the *Journal*, Jun et al. (11) report the results of a meta-analysis of fibrates in the subgroup of patients with baseline CKD. While the authors did not report the baseline TG concentration of the CKD subgroups in these trials, it is expected that the CKD patients would have had a higher TG concentration than the general population due to impaired plasma clearance of VLDL, and thus, could realize a CV benefit from the ~50% TG reduction observed (12). Indeed, in the CKD subgroup, fibrates were associated with a 30% reduction in nonfatal CV events and a 40% reduction in CV death, both of which were statistically significant. At the same time, there was a 14% reduction in the progression of microalbuminuria but an elevation of serum creatinine of ~25%. There was no significant difference in the incidence of end-stage renal disease. Thus, the reduction in renal filtration appeared to lessen albuminuria and elevate serum creatinine but did not impact the progression of CKD to renal replacement therapy.

This report provides further support and clarity on the cardiovascular benefit of fibrates in those with baseline elevated TG and non–HDL-cholesterol. Furthermore, there appears to be a cardiorenal benefit of this class of drugs in reducing renal blood flow and to an extent, attenuating glomerular hyperfiltration and microalbuminuria. In general, fibrates are some of the best tolerated drugs to treat dyslipidemia and the paper by Jun and coworkers supports their use in patients with CKD (7). Clinicians should recognize that using drugs which antagonize the renin-angiotensin system, thereby reducing glomerular filtration, can be protective against the progression of CKD. Future trials should plan a priori cardiorenal endpoints for lipid lowering therapy when off-target pharmacologic effects are possible. In some cases such as fibrates, there can be dual benefits.

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